Chapter 2

Why does ovarian surgery in PCOS help? Insight into the endocrine implications of ovarian surgery for ovulation induction in polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex disorder with heterogeneity of clinical and endocrine features. Ovarian surgery for ovulation induction has been used in the management of clomifene citrate-resistant anovulatory women with PCOS. Various types of ovarian surgery have been employed (wedge resection, electrocautery, laser vaporization, multiple ovarian biopsies and others) and all operations result in an altered endocrine profile after surgery. The mechanism behind the reversal of endocrinological dysfunction in PCOS after ovarian surgery remains incompletely understood. This review scans the literature systematically to identify the endocrine changes after ovarian surgery in PCOS, in order to glean some knowledge of the mechanism involved. After ovarian surgery in PCOS, a rapid reduction of all ovarian hormones is seen, in combination with increased serum levels of pituitary hormones. Folliculogenesis is then initiated and ovarian hormone production increases, synchronically with a reduction of pituitary hormones. Continuation of follicle growth in subsequent cycles after ovarian surgery occurs in an environment with less androgens and lower LH and FSH levels compared with pretreatment levels. The endocrine changes found after ovarian surgery in PCOS women seem to be governed by the ovaries themselves. Rapid reduction of all ovarian hormones restores feedback to the hypothalamus and pituitary, resulting in appropriate gonadotropin secretion. Initiation of follicular development seems to be induced by increasing FSH levels following a reduction of the follicle excess and (intra-ovarian) androgen levels. Additionally, anti-Müllarian hormone and gonadotropin surge attenuating factor probably have a role in the endocrine changes.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility (Adams et al., 1986) and is classically characterized by clinical symptoms of hyperandrogensim (hirsutism and acne) and oligo- or amenorrhoea. The presentation of PCOS symptoms is very heterogeneous, varies from mild to severe and has a wide spectrum. The confusion caused by this heterogeneity of clinical and endocrine features regarding the definition of PCOS will hopefully be settled by the adoption of the recent Rotterdam consensus (2004). Common endocrine abnormalities in PCOS include chronic high luteinising hormone (LH) levels (Berger et al., 1975; Panidis et al., 2005), hyperandrogenism

(Wild et al., 1985; Kumar et al., 2005), hyperinsulinaemia, insulin resistance (Dunaif et al., 1989) and dyslipidoproteinaemia (Wild et al., 1985; Wild, 2002). These endocrine disturbances interfere with folliculogenesis, are (partly) responsible for oligo- or anovulation and are likely to constitute an increased risk for cardiovascular diseases and diabetes (Legro et al., 1999; Elting et al., 2001). In spite of years of research, PCOS remains incompletely understood.

Ovarian surgery for ovulation induction restores the menstrual cycle in the majority of patients suffering from PCOS and favourably changes their endocrine profile (Cohen, 1996). Seventy years after the first report of successful surgical ovarian intervention in PCOS (Stein and Leventhal, 1935), the mechanism behind the reversal of endocrinological dysfunction after ovarian surgery remains unclear. Surgical ovarian intervention for PCOS is sparely used at the present time, as acceptable ovulation and pregnancy rates are achieved using clomifene citrate, metformin and gonadotropins. However, some women remain anovulatory or cannot be successfully treated medically, and ovarian surgery becomes an option.

Types of ovarian surgery

Several surgical approaches for restoring ovulation in women with PCOS have been studied over the years, for example classical wedge resection, multiple ovarian biopsies, laser vaporization and electrocautery. All types of ovarian surgery share a common goal of creating ovarian damage and from an endocrine point of view can be seen as equivalent procedures (Cohen, 1996). A clear distinction has to be made, however, between ovarian drilling to induce ovulation and more extensive ovarian drilling to prevent ovarian stimulation syndrome. The latter method requires more profound ovarian destruction, done by using a lot of power to ‘pepper pot’ the ovaries, whereas the methods for ovulation induction attempt to use the lowest possible dose to achieve the desired effect. Within this review, only the studies with ovarian surgery for ovulation induction are discussed.

Mechanisms involved

The cause for reversal of the endocrinological dysfunction after ovarian surgery in PCOS is unclear. Many theories have been proposed for the cause of the re-establishment of menstrual cycles after ovarian surgery. Originally, the removal of a mechanical barrier has been postulated (Katz et al., 1978; Ben Shlomo et al., 1998) and reducing the size of the ovary was thought to allow gonadotropins to act more effectively after the ovarian surgery (Katz et al., 1978). Others have suggested that surgery may cause increased blood flow to the ovaries, resulting in increased delivery of gonadotropins (Cohen, 1996; Takeuchi et al., 2002). Reduction of androgens after ovarian surgery causes lower peripheral aromatization to estrogens and could theoretically result in restoring feedback to the hypothalamus and pituitary (Felemban et al., 2000; Takeuchi et al., 2002). More recent theories include gonadotropin surge attenuating factor (GnSAF, also called gonadotropin surge inhibiting factor: GnSIF). GnSAF is a hormone produced by the ovaries (Messinis et al., 1991) and its function lies in regulating and suppressing LH secretion by reducing pituitary sensitivity (Fowler et al., 2003). A deficiency of GnSAF in PCOS patients has been hypothesized as the cause of elevated LH levels (Balen and Jacobs, 1991; de Koning et al., 2001). Ovarian surgery could cause increased insulin-like growth factor-I (IGF-I) production, which interacts with follicle stimulating hormone (FSH) and results in follicular development. Follicle growth causes increased GnSAF production, and GnSAF subsequently suppresses LH secretion (Balen and Jacobs, 1994). Another suggested mechanism is reduced inhibin levels after ovarian surgery leading to increased FSH levels (Al Ojaimi, 2004). Less is known about the importance of Anti-Müllarian hormone (AMH) regarding ovarian surgery in PCOS. AMH is an ovarian product and a local inhibitor of FSH action (Durlinger et al., 2001, 2002) and may play a role in restoration of ovulation after ovarian surgery.

No extended review has yet been published to augment the endocrine implications of ovarian surgery and this review combines the existing literature (systematically searched) to identify essential endocrine changes after ovarian surgery in PCOS in order to glean some knowledge of the mechanism involved and further insight into the pathophysiology of PCOS.

MATERIALS AND METHODS

A systematic literature search was conducted in PubMed (January 2006), Embase.com and the Cochrane Library-Wiley (December 2005) databases. Three groups of search terms were used in every possible spelling, as synonyms, acronyms, key- or text words and these groups were combined with an 'AND'-operator. (i) PCOS, (ii) surgical interventions: (electro)cautery, (electro)coagulation, diathermy, drilling, laparoscopic ovarian drilling (LOD), laser, biopsy, excision, wedge, endoscopy, laparoscopy, surgery and (iii) hormones: LH, FSH, testosterone, gonadotropins, gonadotropin releasing hormone (GnRH), prolactin, androgens, androstenedione, dehydroepiandrosterone

(sulphate) (DHEA(S)), dihydrotestosterone (DHT), sex hormone-binding globulin (SHBG), estrogen, progesterone, anti-Müllarian hormone (AMH), gonadotropin surge-inhibiting factor/gonodotrophin surge-attenuating factor (GnSIF/GnSAF), hormones, endocrinology. Case reports and animal-studies were excluded. The full search strategy can be requested from the corresponding author.

A trial was eligible for inclusion if it was a publication in English and the treatment consisted of an ovarian surgery procedure to induce or facilitate ovulation induction in subfertile women with established PCOS, in combination with endocrine results before and after surgery. Study description of characteristics of PCOS subject had to be in accordance with the Rotterdam consensus (2004) criteria. Two reviewers selected the eligible studies, when discordance existed, a uniform decision was made by re-evaluating the study. A total of 63 papers were eligible for this review. Figures shown in this review represent weighted average hormonal values on indicated days, constructed by weighing the mean value of an individual study with their group size (Hazewinkel, 2002) and were constructed when multiple studies were available at different time points to summarize the effect of the surgery. The figures represent an estimate of endocrine changes after ovarian surgery and are shown without units, due to limitations of combining data from different studies with different hormonal assay methodology.

RESULTS

Ovarian hormones

Testosterone and androstenedione

Androgens are frequently and classically elevated in PCOS, with or without clinical symptoms (DeVane et al., 1975; Kumar et al., 2005). The potent androgens testosterone and androstenedione are both secreted by the ovary and the adrenal gland (Burger, 2002) and testosterone is additionally derived from peripheral production (Burger, 2002). Considerable amounts of testosterone are bound to SHBG, only the unbound proportion is biologically active (free) testosterone (Burger, 2002).

Testosterone

Serum testosterone concentrations in PCOS patients decreased after ovarian surgery from post-operative day 1 (Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Greenblatt and Casper, 1987; van der Weiden and Alberda, 1987; van der Weiden et al., 1989; Tasaka et al., 1990; Utsunomiya et al., 1990; Kovacs et al., 1991; Gadir et al., 1992; Campo et al., 1993; Naether et al., 1993; Liguori et al., 1996; Parsanezhad et al., 2005). One study showed a non-significant decrease one day after surgery (Kojima et al., 1989). One study showed increased testosterone values three hours after surgery preceding a rapid decrease on the first postoperative day (Judd et al., 1976). Testosterone concentrations reached a nadir around

3 days after surgery (Greenblatt and Casper, 1987; Campo et al., 1993; Liguori et al., 1996), followed by a small increase, but never reaching pretreatment values.

In the first days, weeks and years following ovarian surgery, testosterone levels remained low in the majority of the studies (Vejlsted and Albrechtsen, 1976; Aakvaag and Gjonnaess, 1985; Greenblatt and Casper, 1987; van der Weiden and Alberda, 1987; Sumioki et al., 1988; van der Weiden et al., 1989; Armar et al., 1990; Gadir et al., 1990; Keckstein et al., 1990; Tasaka et al., 1990; Utsunomiya et al., 1990; Kovacs et al., 1991; Rossmanith et al., 1991; Abdel et al., 1993; Campo et al., 1993; Naether et al., 1993; Tiitinen et al., 1993; Verhelst et al., 1993; Alborzi, 1994; Liguori et al., 1996; Taskin et al., 1996; Anttila et al., 1998; Gjonnaess, 1998, 1999; Kaaijk et al., 1999; Soliman et al., 2000; Wu et al., 2000, 2004; Zullo et al., 2000; Alborzi et al., 2001; Amer et al., 2002a; Asada et al., 2002; Takeuchi et al., 2002; Amin et al., 2003; Duleba et al., 2003; Malkawi et al., 2003; Parsanezhad et al., 2003; Al Ojaimi, 2004; Api et al., 2005; Kucuk and Kilic-Okman, 2005; Malkawi and Qublan, 2005; Parsanezhad et al., 2005). A few studies found no change in testosterone concentrations after ovarian surgery (Campo et al., 1983; Kojima et al., 1989; Szilagyi et al., 1990; Farhi et al., 1995; Fukaya et al., 1995; Farquhar et al., 2002). Although most studies did not find differences in baseline and/or post-treatment testosterone values between post-treatment ovulatory and non-ovulatory women, between pregnant and nonpregnant women or between obese versus lean patients (Abdel et al., 1993; Campo et al., 1993; Duleba et al., 2003; Al Ojaimi, 2004; Wu et al., 2004; Parsanezhad et al., 2005), some studies did find lower (Aakvaag and Gjonnaess, 1985; Amer et al., 2003b; Api et al., 2005; Hayashi et al., 2005; Kucuk and Kilic-Okman, 2005) or higher (Farhi et al., 1995) testosterone concentrations pre- and/or post-operatively in post-treatment ovulatory PCOS women.

A dose/'puncture' response relationship was found in one study, showing lower testosterone levels after surgery when using more punctures. This relationship was seen using low numbers of punctures per ovary (Amer et al., 2003a), but was not found in a study using more punctures (Malkawi and Qublan, 2005).

Regularly ovulating controls undergoing diagnostic laparoscopy or laparoscopic tubal ligation showed no testosterone change in the first days to weeks after surgery in two studies (Greenblatt and Casper, 1987; Liguori et al., 1996). However, other studies found a testosterone decrease after surgery in controls, although less marked than in PCOS women (Gjonnaess and Norman, 1987; Utsunomiya et al., 1990; Parsanezhad et al., 2005).

Overall, profound reduction of testosterone was seen from the first day after ovarian surgery. Testosterone levels reached a nadir around the third post-operative day and thereafter increased gradually, without reaching pre-operative values (Figure 1A). Responders to ovarian surgery

seemed to have comparable pre- and post-treatment testosterone concentrations compared with non-responders (Figure 1B), although some studies gave conflicting results. The reduction of testosterone seemed to be dose dependent (the more tissue destruction, the lower the testosterone levels after surgery), although this relationship was only found using low numbers of punctures per ovary and a maximal testosterone reduction was quickly reached.

Regularly ovulating controls showed a slight decline of androgens after laparoscopic surgery, but this was less marked than that in PCOS women (Figure 1A).

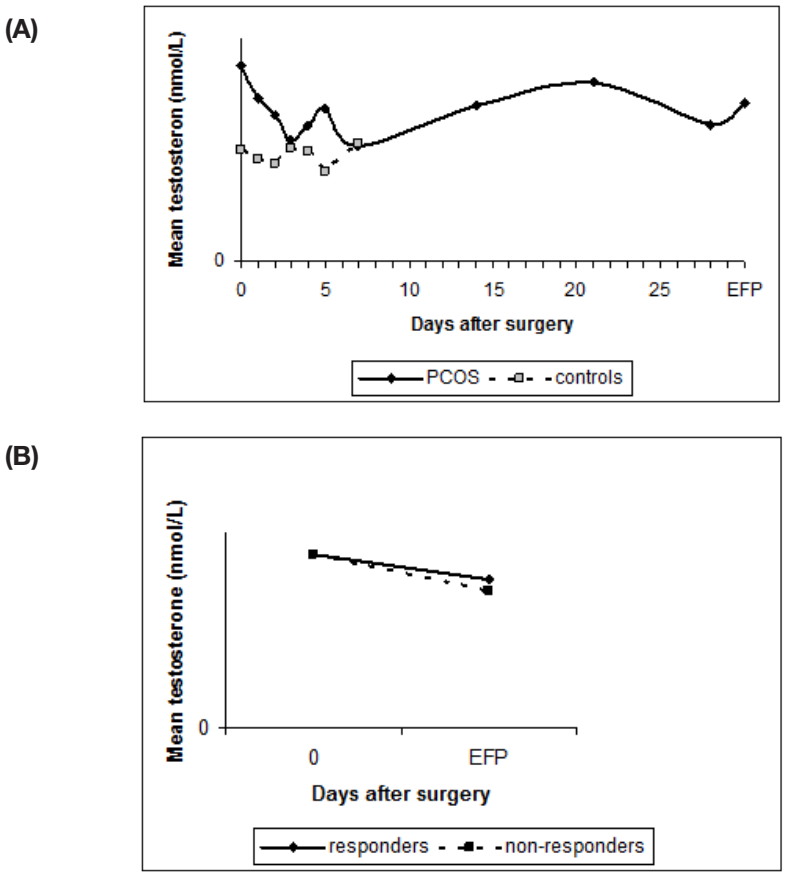

Figure 1. (A) Mean testosterone serum levels (nmol/L) in polycystic ovary syndrome (PCOS) women and regularly ovulating controls prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase (EFP). PCOS values are derived from 35 papers, a maximum of 1123 patients and control values from 6 papers with a maximum of 121 patients.
(B) Mean testosterone serum levels (nmol/L) in post-treatment PCOS responders and non-responders. Shown are data from prior to ovarian surgery (days=0) and in the subsequent EFP after ovarian surgery. Values are derived from 9 papers and a maximum of 307 responders and 109 non-responders.

Androstenedione

Serum androstenedione levels decreased significantly in the first days after treatment in most studies (Judd et al., 1976; Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Greenblatt and Casper, 1987; Sumioki et al., 1988; Kojima et al., 1989; van der Weiden et al., 1989; Armar et al., 1990; Sakata et al., 1990; Szilagyi et al., 1990; Campo et al., 1993; Liguori et al., 1996; Zullo et al., 2000), although two studies found a non-significant reduction (van der Weiden and Alberda, 1987; Utsunomiya et al., 1990). Androstenedione levels during the surgical procedure increased in both PCOS women (Judd et al., 1976; Armar et al., 1990) and regularly ovulating controls (Judd et al., 1976). A nadir was reached 2–4 days after treatment (Judd et al., 1976; Greenblatt and Casper, 1987; Armar et al., 1990; Sakata et al., 1990; Campo et al., 1993; Liguori et al., 1996).

Week(s) to years after ovarian surgery, androstenedione levels in PCOS remained low, although there was a tendency to increase slightly over time (Judd et al., 1976; Aakvaag and Gjonnaess, 1985; Greenblatt and Casper, 1987; van der Weiden and Alberda, 1987; Sumioki et al., 1988; Kojima et al., 1989; van der Weiden et al., 1989; Armar et al., 1990; Keckstein et al., 1990; Sakata et al., 1990; Rossmanith et al., 1991; Campo et al., 1993; Szilagyi et al., 1993; Tiitinen et al., 1993; Verhelst et al., 1993; Taskin et al., 1996; Anttila et al., 1998; Gjonnaess, 1998, 1999; Wu et al., 2000; Amer et al., 2002a, 2003a; Malkawi et al., 2003; Malkawi and Qublan, 2005). A few studies showed no androstenedione change following ovarian surgery (Utsunomiya et al., 1990; Kovacs et al., 1991; Cibula et al., 2000). Post-treatment ovulatory women showed lower androstenedione levels prior to and after surgery compared with non-responders (Aakvaag and Gjonnaess, 1985). A dose/'puncture' response relationship was found in one study, showing lower androstenedione levels after surgery when using more punctures. Comparable to testosterone, the dose response relationship for androstenedione was seen using low numbers of punctures per ovary (Amer et al., 2003a), but was not found in a study using more punctures (Malkawi and Qublan, 2005).

Regularly ovulating controls showed no change of androstenedione levels after surgery (Judd et al., 1976; Utsunomiya et al., 1990; Liguori et al., 1996; Amer et al., 2002a), although one study found decreased levels after treatment (Gjonnaess and Norman, 1987).

To summarize, reduction of androstenedione in PCOS was seen from the first day after ovarian surgery, but during the ovarian surgery elevated androstenedione levels were found. Androstenedione levels reached a nadir around the fourth post-operative day, and thereafter androgen values increased gradually (Figure 2). PCOS patients responding to ovarian surgery seem to have lower pre- and post-treatment androstenedione values compared with non-responders (no figure due to limited numbers of studies). Reduction of androstenedione could be dose dependent, although this relationship was only found using low numbers of punctures per ovary. Regularly ovulating controls showed no change of androstenedione after laparoscopic surgery (Figure 2).

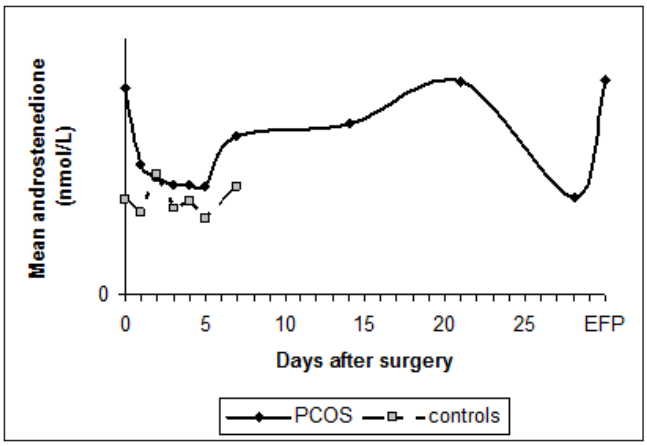

Figure 2. Mean androstenedione serum levels (nmol/L) in PCOS women and regularly ovulating controls prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. PCOS values are derived from 25 papers, a maximum of 454 patients and control values from 5 papers with a maximum of 91 patients.

Estradiol

Ovarian granulosa cells produce estrogens in response to FSH stimulation (Havelock et al., 2004). Women with PCOS frequently have chronic stable estrogen levels due to insufficient follicle growth.

Estradiol concentrations remained stable in the first days following ovarian surgery in PCOS women in most studies (Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Sumioki et al., 1988; Kojima et al., 1989; van der Weiden et al., 1989; Sakata et al., 1990; Szilagyi et al., 1990; Utsunomiya et al., 1990; Abdel et al., 1993), although decreased levels were also found (Judd et al., 1976; Tanaka et al., 1978; Greenblatt and Casper, 1987). Early and mid follicular estradiol concentrations weeks after surgery were comparable to pretreatment levels (van der Weiden et al., 1989; Gadir et al., 1990; Sakata et al., 1990; Tasaka et al., 1990; Verhelst et al., 1993; Wu et al., 2004; Kucuk and Kilic-Okman, 2005; Kandil and Selim, 2005) or were decreased (Rossmanith et al., 1991; Szilagyi et al., 1993).

Late follicular, peri-ovulatory and luteal estrogen levels were higher than before ovarian surgery, especially in responders (Aakvaag and Gjonnaess, 1985; Kojima et al., 1989; Verhelst et al., 1993; Gjonnaess, 1998). Many studies compared pre- and post-treatment estradiol measurements without mentioning the cycle days. These studies will not be discussed here, because results cannot be interpreted.

Regularly ovulating controls showed no estradiol change following surgery (Gjonnaess and Norman, 1987).

Overall, estradiol decreased slightly in the first days after surgery, followed by an increase approximately three weeks after treatment (Figure 3A). The early follicular estradiol levels in subsequent cycles were slightly decreased compared with pretreatment values. Peri-ovulatory and luteal estradiol concentrations were increased, especially in responders (Figure 3B).

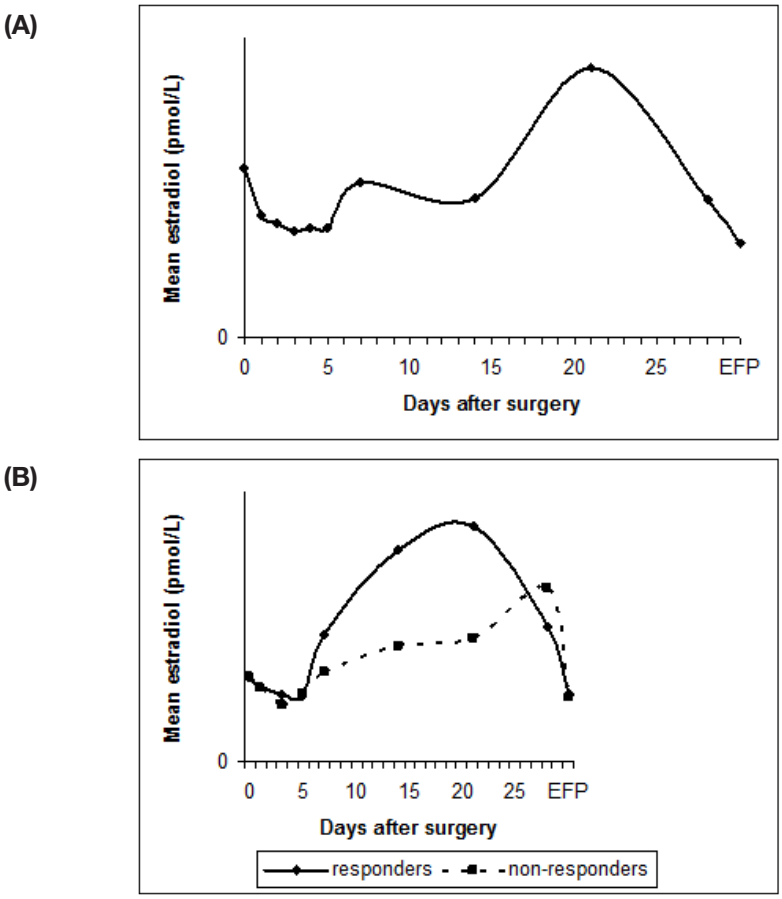

Figure 3. (A) Mean estradiol serum levels (pmol/L) in PCOS women prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 13 papers and a maximum of 139 patients.
(B) Mean estradiol serum levels (pmol/L) in posttreatment PCOS responders and non-responders. Shown are data from prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 3 papers and a maximum of 73 responders and 23 non-responders.

Inhibins

Inhibins are produced by granulosa cells and production is stimulated by FSH, and inhibins, in turn, inhibit FSH secretion (Laven and Fauser, 2004). Inhibin B is mainly produced by pre- and small antral follicles and concentrations are highest in the midfollicular phase (Laven and Fauser, 2004). Women with PCOS have inhibin B levels within the normal range (Magoffin and Jakimiuk, 1998; Norman et al., 2001; Cortet-Rudelli et al., 2002; Welt et al., 2002), in spite of many small follicles. It has been speculated that inhibin levels in PCOS are relatively suppressed by LH and insulin (Welt et al., 2002).

Three studies reported inhibin levels before and after ovarian surgery. Pre-operatively inhibin B levels on cycle day 5 were higher than in regularly ovulating controls and no pattern of regular pulsatility was seen (Lockwood et al., 1998). A rapid decrease of inhibin post-operatively followed by a subsequent rise (maximum at 3 weeks) was found by Kovacs et al. (1991) (although this study did not define its PCOS population used), and initiation of inhibin B pulsatility was seen after ovarian surgery (Lockwood et al., 1998).

Two studies showed lower inhibin B levels in the early follicular phase, 1–3 months after bilateral drilling or diathermy (Lockwood et al., 1998; Kandil and Selim, 2005) whereas no significant change was seen after unilateral drilling (Kandil and Selim, 2005).

Inhibin levels seem to decrease rapidly after ovarian surgery, followed by a subsequent rise and restoration of inhibin pulsatility. Inhibin levels rose 3–5 weeks after ovarian surgery. Early follicular phase levels in subsequent cycles after ovarian surgery showed lower inhibin levels. Due to limited studies measuring inhibin after surgery, it was not possible to compose a figure.

Progesterone

Progesterone is produced by luteinized granulosa cells under LH stimulation (Havelock et al., 2004).

Progesterone concentrations remained stable for up to 2 weeks after ovarian surgery and in subsequent follicular phases (Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Verhelst et al., 1993; Wu et al., 2004). One study showed a decline of progesterone 8 days after surgery in ovulatory women (Armar et al., 1990). Approximately 3 weeks after ovarian surgery and in following luteal phases, progesterone levels rose and were higher than pretreatment values (Aakvaag and Gjonnaess, 1985; Verhelst et al., 1993; Gjonnaess, 1998, 1999).

Progesterone levels in regularly ovulating controls did not show changes after surgery (Gjonnaess and Norman, 1987).

Ovarian surgery does not seem to influence progesterone levels directly after the procedure (Figure 4A and 4B). Weeks after the treatment, progesterone levels rose temporarily in patients responding to surgery and returned to pretreatment levels in subsequent follicular phases.

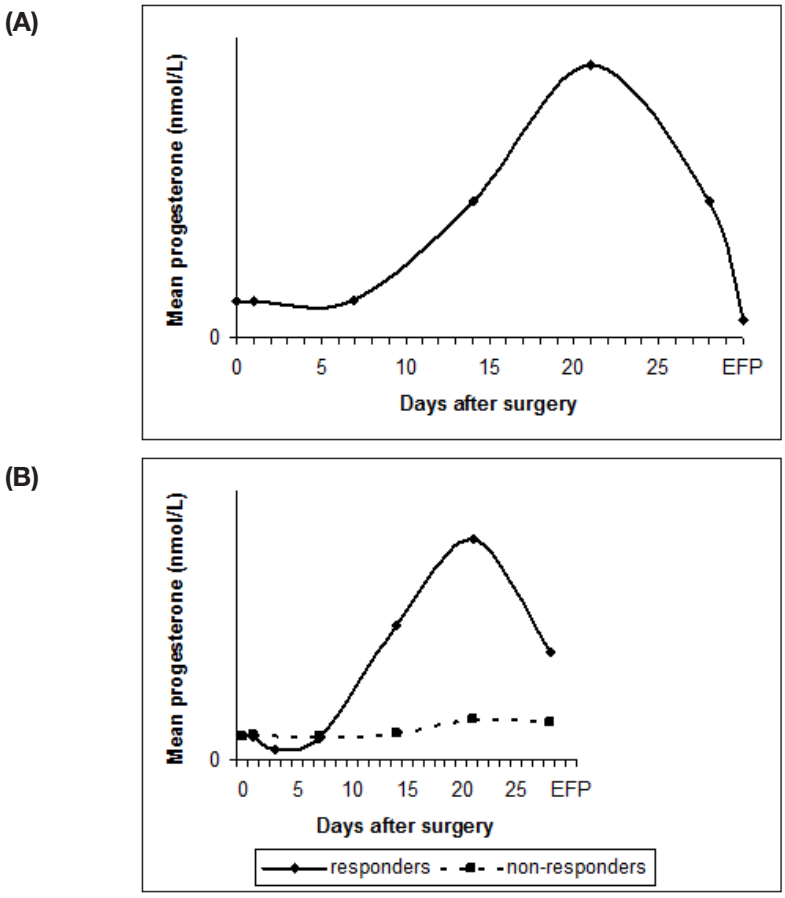

Figure 4. (A) Mean progesterone serum levels (nmol/L) in PCOS women prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 4 papers and a maximum of 109 patients.
(B) Mean progesterone serum levels (nmol/L) in post-treatment PCOS responders and non-responders. Shown are data from prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 2 papers and a maximum of 51 responders and 16 non-responders.

Anti-Müllarian hormone

AMH is an ovarian product, a marker of ovarian reserve (van Rooij et al., 2002, 2005) and is a local inhibitor of FSH action (Durlinger et al., 2001, 2002). Ovarian production of AMH is higher in PCOS patients compared with women with regular menstrual cycles (Cook et al., 2002; Pigny et al., 2006), probably due to an excess of antral follicles (Jonard and Dewailly, 2004).

So far, no studies have been published about the possible AMH changes after ovarian surgery in PCOS.

Pituitary hormones

Luteinising hormone

LH stimulates androstenedione production by ovarian theca cells (Havelock et al., 2004) and is responsible for ovulation and luteinization. Chronically elevated LH concentrations are common and characteristic of women with PCOS (van Santbrink et al., 1997) and are (partly) responsible for the problems associated with this syndrome.

The day after ovarian surgery, LH concentrations in PCOS women increased in most studies (Gjonnaess and Norman, 1987; Greenblatt and Casper, 1987; Sakata et al., 1990; Tasaka et al., 1990; Naether et al., 1993; Liguori et al., 1996), although no (significant) change (Judd et al., 1976; Kojima et al., 1989; van der Weiden et al., 1989; Utsunomiya et al., 1990; Abdel et al., 1993; Campo et al., 1993) and an LH decrease were also found (Parsanezhad et al., 2005). Subsequently, LH levels decreased and remained low (with the exception of peri-ovulatory peaks) for years after surgery (Tanaka et al., 1978; Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Greenblatt and Casper, 1987; Sumioki et al., 1988; van der Weiden et al., 1989; Armar et al., 1990; Gadir et al., 1990, 1992; Sakata et al., 1990; Tasaka et al., 1990; Rossmanith et al., 1991; Szilagyi et al., 1993; Tiitinen et al., 1993; Alborzi, 1994; Farhi et al., 1995; Fukaya et al., 1995; Liguori et al., 1996; Taskin et al., 1996; Anttila et al., 1998; Gjonnaess, 1998, 1999; Soliman et al., 2000; Wu et al., 2000, 2004; Zullo et al., 2000; Alborzi et al., 2001; Amer et al., 2002a, b, 2003a, b; Takeuchi et al., 2002; Amin et al., 2003; Duleba et al., 2003; Malkawi et al., 2003; Parsanezhad et al., 2003; Al Ojaimi, 2004; Kamel et al., 2004; Api et al., 2005; Kucuk and Kilic-Okman, 2005; Malkawi and Qublan, 2005; Parsanezhad et al., 2005). A few studies found unchanged LH levels weeks to months after surgery or increased LH values (mostly peri-ovulatory measurements) (Judd et al., 1976; Kojima et al., 1989; Szilagyi et al., 1990; Utsunomiya et al., 1990; Kovacs et al., 1991; Campo et al., 1993; Naether et al., 1993; Verhelst et al., 1993; Cibula et al., 2000; Asada et al., 2002).

Baseline LH values were higher in women who responded to surgery (Al Ojaimi, 2004; Hayashi et al., 2005) and in lean women (Wu et al., 2004), whereas others found no differences (Duleba

et al., 2003) or lower LH values in responders (Api et al., 2005). The magnitude of the LH-decrease after surgery was higher in PCOS responders (ovulatory or pregnant) compared with non-responders (Aakvaag and Gjonnaess, 1985; Abdel et al., 1993; Jamal, 2000; Amer et al., 2003b; Parsanezhad et al., 2003; Al Ojaimi, 2004; Api et al., 2005; Hayashi et al., 2005).

A dose/'puncture' dependency was found, showing a more pronounced increase in LH levels after surgery when using more punctures. This relationship was seen using a small number of punctures per ovary (Amer et al., 2002b, 2003a), but this was not shown with more punctures (Malkawi and Qublan, 2005). After surgery, the LH amplitude decreased while the frequency remained stable (Sumioki et al., 1988; Rossmanith et al., 1991). Regularly ovulating controls did not show LH change after surgery (Judd et al., 1976; Gjonnaess and Norman, 1987; Utsunomiya et al., 1990; Amer et al., 2002a; Parsanezhad et al., 2005).

Thus LH concentrations showed a transient increase the day after ovarian surgery in PCOS, followed by a gradual decrease (Figure 5A). Weeks to years after ovarian surgery, LH levels remained low, with the exception of peri-ovulatory peaks. Lower LH pulse amplitude seems to cause the lower LH levels, while the LH pulse frequency remained stable. Minimal ovarian damage was needed to lower the LH concentrations and a possible dose response relationship was seen. Both responders to ovarian surgery and non-responders showed an LH increase the day after surgery. PCOS women responding to ovarian surgery showed a more pronounced decline of LH levels in the early follicular phase after the procedure compared with non-responders (Figure 5B).

Follicle stimulating hormone

FSH stimulates granulosa cell production of estradiol, inhibin B and GnSAF (Messinis et al., 1991; Havelock et al., 2004; Laven and Fauser, 2004). Increasing pituitary FSH production during the early follicular phase allows the growth of a follicle cohort. Anovulation in PCOS is thought to be partly due to a relative intrinsic inhibition of FSH action. The follicular arrest can be reversed by increasing the amount of FSH by FSH supplementation or stimulation of endogenous FSH production by clomifene citrate administration. Pituitary FSH secretion is selectively suppressed by inhibin A and B (Laven and Fauser, 2004).

FSH levels rose in the first days after ovarian surgery in women with PCOS (Greenblatt and Casper, 1987; Sakata et al., 1990; Tasaka et al., 1990; Naether et al., 1993; Liguori et al., 1996; Parsanezhad et al., 2003), although some studies found no (significant) change (Judd et al., 1976; Gjonnaess and Norman, 1987; Kojima et al., 1989; van der Weiden et al., 1989; Utsunomiya et al., 1990; Campo et al., 1993; Parsanezhad et al., 2005).

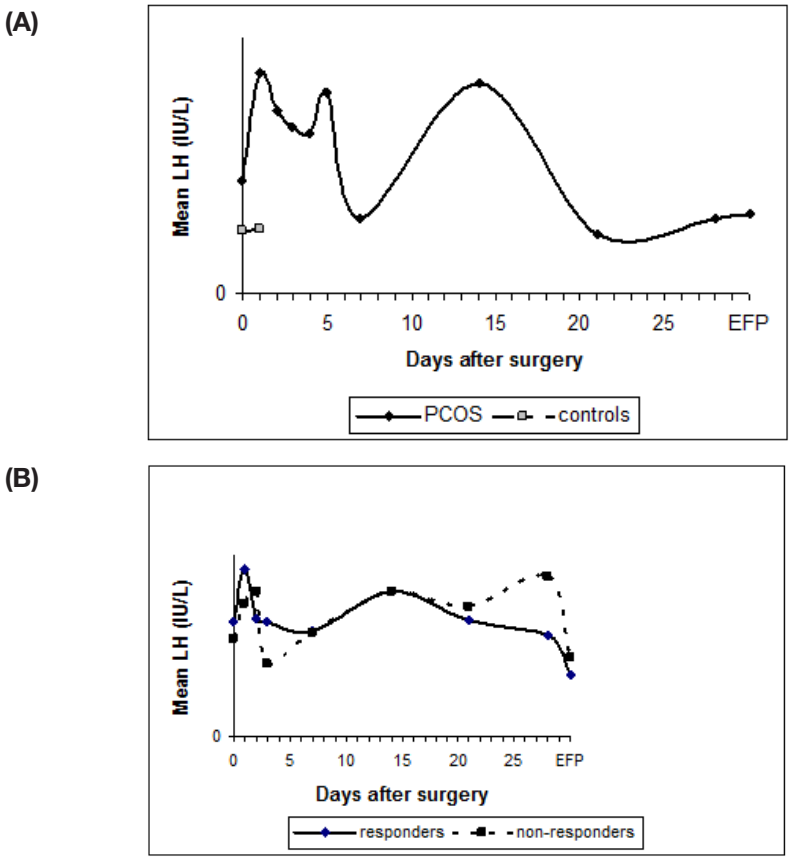

Figure 5. (A) Mean luteinising hormone (LH) serum levels (IU/L) in PCOS women and regularly ovulating controls prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. PCOS values are derived from 38 papers, a maximum of 1127 patients and control values from 4 papers with a maximum of 65 patients.
(B) Mean LH serum levels (IU/L) in post-treatment PCOS responders and non-responders. Shown are data from prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 10 papers and a maximum of 311 responders and 106 non-responders.

In the first weeks after surgery, FSH concentrations declined to levels comparable to baseline values (Judd et al., 1976; Tanaka et al., 1978; Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Greenblatt and Casper, 1987; Sumioki et al., 1988; Kojima et al., 1989; Armar et al., 1990; Sakata et al., 1990; Szilagyi et al., 1990, 1993; Tasaka et al., 1990; Kovacs et al., 1991; Campo et al., 1993; Naether et al., 1993; Tiitinen et al., 1993; Verhelst et al., 1993; Alborzi,

1994; Farhi et al., 1995; Fukaya et al., 1995; Liguori et al., 1996; Anttila et al., 1998; Soliman et al., 2000; Wu et al., 2000, 2004; Zullo et al., 2000; Amer et al., 2002a, 2003a, b; Takeuchi et al., 2002; Duleba et al., 2003; Malkawi et al., 2003; Kandil and Selim, 2005; Kucuk and Kilic-Okman, 2005; Malkawi and Qublan, 2005; Parsanezhad et al., 2005), whereas others found increased (van der Weiden et al., 1989; Gadir et al., 1990; Utsunomiya et al., 1990; Rossmanith et al., 1991; Abdel et al., 1993; Taskin et al., 1996; Amer et al., 2002b; Amin et al., 2003; Parsanezhad et al., 2003; Al Ojaimi, 2004; Kamel et al., 2004; Api et al., 2005) or decreased (Szilagyi et al., 1990; Gjonnaess, 1998, 1999; Alborzi et al., 2001) FSH values after ovarian surgery.

A dose/'puncture' dependency was not found (Amer et al., 2003a; Malkawi and Qublan, 2005), although one study showed a possible trend towards higher FSH levels when using more punctures (Amer et al., 2002b). FSH pulse frequency and amplitude did not change after the treatment (Sumioki et al., 1988; Rossmanith et al., 1991).

PCOS responders showed a more pronounced increase in FSH in the first days after surgery compared with non-responders (Aakvaag and Gjonnaess, 1985; Armar et al., 1990; Abdel et al., 1993; Campo et al., 1993). In most studies, FSH values in the weeks after surgery were comparable between responders and non-responders and the initial difference seen after surgery was lost (Jamal, 2000; Amer et al., 2003b; Al Ojaimi, 2004; Api et al., 2005), although one study found elevated FSH in responders (Parsanezhad et al., 2003) and another in non-responders (Hayashi et al., 2005).

Regularly ovulating controls showed no FSH change after surgery (Judd et al., 1976; Gjonnaess and Norman, 1987; Utsunomiya et al., 1990; Amer et al., 2002a; Parsanezhad et al., 2005).

Overall, FSH concentrations increased in the first days after ovarian surgery, with a more pronounced elevation in responders (Figures 6A and 6B). Following this FSH elevation, the levels returned gradually to pre-operative values and the initial difference shortly after surgery between responders and non-responders was lost (Figure 6B). FSH pulsatility did not change after surgery.

Prolactin

Prolactin is mainly secreted by the anterior pituitary and secretion is under the tonic inhibition of dopamine. Prolactin has a diurnal variation and various factors like estrogens and (surgical) stress stimulate prolactin secretion (Tyson et al., 1972; Sassin et al., 1973; Brandt et al., 1976). Studies with large PCOS populations showed average prolactin levels within the (high) normal range (Balen et al., 1995; Hernandez et al., 2000). In spite of normal prolactin levels in PCOS, the reaction to a dopamine receptor antagonist (metoclopramide) is less than in ovulatory controls, suggesting a low dopamine hypothalamic tone (Minakami et al., 1988; Hernandez et al., 2000).

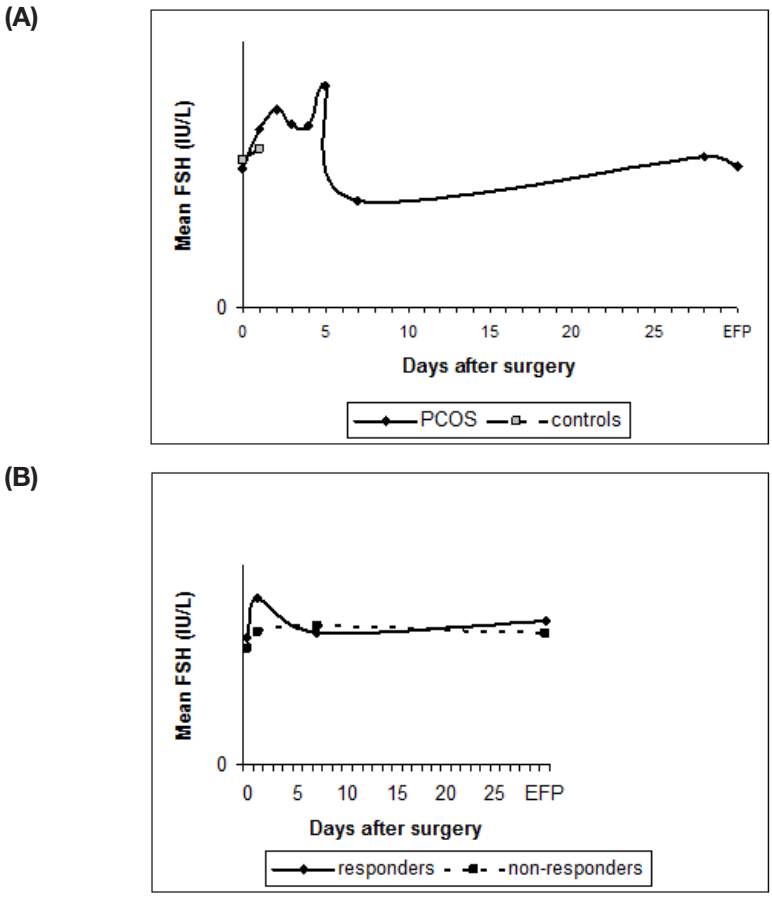

Figure 6. (A) Mean follicle stimulating hormone (FSH) serum levels (IU/L) in PCOS women and regularly ovulating controls prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. PCOS values are derived from 34 papers, a maximum of 1092 patients and control values from 4 papers with a maximum of 60 patients.
(B) Mean FSH serum levels (IU/L) in post-treatment PCOS responders and non-responders. Shown are data from prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. Values are derived from 8 papers and a maximum of 302 responders and 103 non-responders.

After surgery, prolactin levels rose on the first day in both PCOS patients and in ovulatory controls (Gjonnaess and Norman, 1987; van der Weiden et al., 1989; Parsanezhad et al., 2005). Prolactin concentrations were not altered weeks to years after the procedure in the majority of the studies (van der Weiden et al., 1989; Gadir et al., 1990; Szilagyi et al., 1990; Verhelst et al., 1993; Gjonnaess, 1998; Alborzi et al., 2001; Duleba et al., 2003; Al Ojaimi, 2004; Wu et al.,

2004; Kucuk and Kilic-Okman, 2005). One study showed a decline in prolactin after the ovarian procedure (Alborzi, 1994), another study an increase in prolactin up to 10 weeks after ovarian surgery (Parsanezhad et al., 2005). Parsanezhad et al. (2005) showed that the majority of the women remaining anovulatory after ovarian surgery were hyperprolactinaemic 6–10 weeks after surgery. Prolactin response to dopaminergic blockade by metoclopramide was increased after ovarian surgery (Szilagyi et al., 1993).

A transient prolactin elevation after surgery was seen in both PCOS patients and in regularly ovulatory controls. Ovarian surgery does not seem to influence basal prolactin levels weeks to months after the procedure, although dopaminergic inhibition of prolactin seems to increase as indicated by the increased response to metoclopramide.

Gonadotropin releasing hormone challenge test

The sensitivity and priming of the pituitary to gonadotropin releasing hormone (GnRH or LHRH) can be measured by the magnitude of FSH and LH response to GnRH administration. Patients with PCOS have a higher LH response to GnRH compared with ovulatory controls (Heineman et al., 1984). This suggests that in women with PCOS the pituitary is already primed. The cause of this increased sensitivity of the pituitary in PCOS is unclear. It has been suggested that the low concentrations of the ovarian hormone GnSAF may be responsible for this priming. GnSAF normally antagonizes the priming (Fowler et al., 1990; Dafopoulos et al., 2004).

Ovarian surgery diminished pituitary LH response to GnRH administration in the first weeks after ovarian surgery in PCOS (Tanaka et al., 1978; Sumioki et al., 1988; Keckstein et al., 1990; Mio et al., 1991; Rossmanith et al., 1991; Campo et al., 1993; Fukaya et al., 1995). Only on the first day after surgery was the LH response to GnRH found to be increased (Gjonnaess and Norman, 1987).

Adrenal hormones

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEAS) act as inactive precursor steroids for peripheral conversion into more potent androgens (Burger, 2002; Labrie et al., 2005). They are predominantly of adrenocortical origin and are frequently elevated in PCOS (DeVane et al., 1975; Kumar et al., 2005). Due to its adrenocortical origin, DHEAS is used as a marker for adrenal androgen production (Kumar et al., 2005).

In the first days after ovarian surgery, DHEA(S) levels decreased in half of the studies (Gjonnaess and Norman, 1987; Szilagyi et al., 1990; Utsunomiya et al., 1990; Liguori et al., 1996), whereas the other studies showed no significant change (Aakvaag and Gjonnaess, 1985; Naether et al., 1993; Cibula et al., 2000; Parsanezhad et al., 2005).

Weeks to months after ovarian surgery, DHEAS and/or DHEA levels were comparable with pre-operative values in the majority of the studies (Vejlsted and Albrechtsen, 1976; Campo et al., 1983; Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987; Sumioki et al., 1988; Armar et al., 1990; Szilagyi et al., 1990; Utsunomiya et al., 1990; Kovacs et al., 1991; Rossmanith et al., 1991; Naether et al., 1993; Tiitinen et al., 1993; Verhelst et al., 1993; Gjonnaess, 1998; Cibula et al., 2000; Wu et al., 2000, 2004; Takeuchi et al., 2002; Duleba et al., 2003; Api et al., 2005; Kucuk and Kilic-Okman, 2005; Parsanezhad et al., 2005), although some studies showed decreased DHEA(S) levels (Naether et al., 1993; Liguori et al., 1996; Gjonnaess, 1999; Alborzi et al., 2001; Malkawi et al., 2003; Malkawi and Qublan, 2005).

No differences in DHEAS levels before and/or after surgery were found between the post-treatment ovulatory group compared with the non-ovulatory group (Aakvaag and Gjonnaess, 1985; Parsanezhad et al., 2005), between the patients who became pregnant compared with the non-pregnant women (Duleba et al., 2003; Cleemann et al., 2004; Api et al., 2005) and the obese versus lean patients (Wu et al., 2004).

DHEAS levels in control groups with regularly ovulatory women undergoing laparoscopy varied from a decrease the first days after surgery (Gjonnaess and Norman, 1987; Utsunomiya et al., 1990) to no change for up to months after laparoscopy (Parsanezhad et al., 2005).

Thus, the influence of ovarian surgery on DHEA(S) production seems unclear. Overall, the DHEA(S) levels seems to decrease slightly in the first days following surgery (Figure 7). This was seen in both PCOS women and in controls. Weeks to months after the treatment, DHEA(S) levels were comparable or slightly reduced in PCOS patients. DHEAS levels before and after surgery did not differ between responders and non-responders and between lean and obese patients.

Cortisol and ACTH testing

Cortisol levels remained stable in three studies measuring cortisol levels for up to months after ovarian surgery (Sumioki et al., 1988; Gadir et al., 1990; Wu et al., 2000).

The adrenal steroid response (17-hydroxy (OH) progesterone, androstenedione, DHEA(S) and cortisol) to adrenocorticotropic hormone (ACTH) was not influenced by ovarian surgery in two studies (Cibula et al., 2000; Saleh et al., 2001). Another study showed lower 17 ketosteroid, 17-OH progesterone and androstenedione secretions as a response to ACTH stimulation after ovarian surgery (Wu et al., 2000).

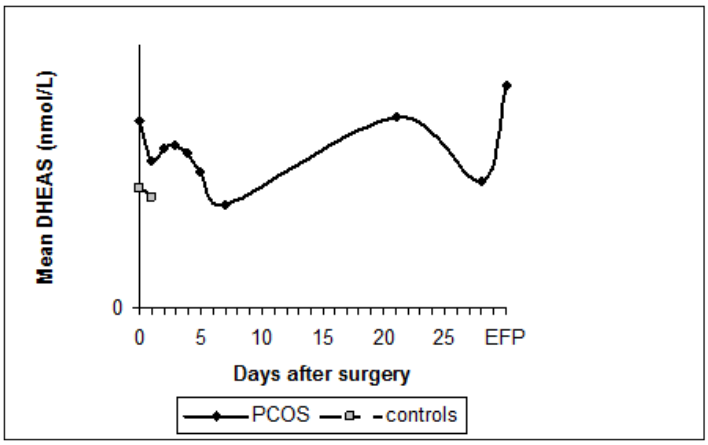

Figure 7. Mean dehydroepiandrosterone (DHEAS) serum levels (nmol/L) in PCOS women and in regularly ovulating controls prior to ovarian surgery (days=0), the first 28 days following ovarian surgery and in the subsequent early follicular phase. PCOS values are derived from 18 papers, a maximum of 806 patients and control values from 3 papers with a maximum of 60 patients.

17-hydroxy progesterone

17-OH progesterone decreased on the first day after ovarian surgery in women with PCOS and in regularly ovulating controls (Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987). Subsequently 17-OH progesterone levels returned in PCOS women to pretreatment values (Aakvaag and Gjonnaess, 1985; Verhelst et al., 1993; Malkawi et al., 2003; Malkawi and Qublan, 2005), although one study showed an increase in 17-OH progesterone (Gjonnaess, 1998).

Other hormones

Dihydrotestosterone

DHT is a potent androgenic metabolite and is primarily derived from peripheral conversion (through enzyme 5-alpha-reductase) of testosterone, androstenedione and DHEA and is partly secreted by the adrenal gland (Silva et al., 1987; Burger, 2002). Increased 5-alpha-reductase activity is found in PCOS and could (partly) be responsible for excess DHT production in PCOS (Fassnacht et al., 2003; Jakimiuk et al., 1999). Besides substantial ovarian and adrenal production of androgens, increased peripheral conversion contributes to higher total androgen levels in PCOS (Fassnacht et al., 2003).

On the first day after ovarian surgery, DHT levels decreased in both PCOS patients and in ovulatory controls (in the follicular phase) (Aakvaag and Gjonnaess, 1985; Gjonnaess and Norman, 1987). Weeks to years after ovarian surgery, DHT levels remained stable (Aakvaag and Gjonnaess, 1985; Gjonnaess, 1999) or alternated within the same study between normal and

lower values (Verhelst et al., 1993: Gjonnaess, 1998). Post-treatment ovulatory women showed lower pretreatment DHT values than non-ovulatory women (Aakvaag and Gjonnaess, 1985).

Overall DHT concentration decreased the day after surgery in both PCOS patients and ovulatory controls. After the initial reduction, DHT levels returned to pre-operative values or remained decreased.

Sex hormone binding globulin

SHBG is a major transport protein for testosterone and its production is inhibited by insulin and prolactin and stimulated by testosterone and estradiol (Plymate et al., 1988). Women with PCOS show lower serum levels of SHBG than ovulatory controls (Kumar et al., 2005).

Most studies showed no significant change in SHBG concentrations after ovarian surgery in PCOS women (Judd et al., 1976; Gjonnaess and Norman, 1987; van der Weiden et al., 1989; Szilagyi et al., 1990; Kovacs et al., 1991; Rossmanith et al., 1991; Tiitinen et al., 1993; Verhelst et al., 1993; Taskin et al., 1996; Anttila et al., 1998; Wu et al., 2000; Amer et al., 2003a; Duleba et al., 2003), although increased SHBG levels were sometimes found after surgery (Aakvaag and Gjonnaess, 1985; Gjonnaess, 1998, 1999; Wu et al., 2004; Kucuk and Kilic-Okman, 2005). Overall SHBG levels seem to increase modestly after ovarian surgery.

Insulin, glucose and insulin resistance

PCOS women often have some degree of insulin resistance and compensatory hyperinsulinaemia (Dunaif et al., 1989; Legro et al., 2004). Insulin increases the GnRH stimulated LH release, potentiates LH-induced ovarian androgen synthesis (Adashi et al., 1981; Bergh et al., 1993) and has a role in the pathogenesis of PCOS. The gold standard for whole-body insulin sensitivity assessment is the euglycemic–hyperinsulinaemic clamp (Legro et al., 2004). Unfortunately, this test is time consuming and expensive and the oral glucose tolerance tests (OGTT) is the best practical alternative (Legro et al., 2004).

Fasting insulin levels in PCOS patients remained unaltered in the first weeks to months after ovarian surgery in the majority of the studies (Tiitinen et al., 1993; Tulandi et al., 2000; Saleh et al., 2001; Duleba et al., 2003; Malkawi et al., 2003; Wu et al., 2004; Malkawi and Qublan, 2005). Two studies showed a small, but significant decline of fasting insulin levels one and six months after ovarian surgery (Wu et al., 2000; Api et al., 2005).

One study showed a rise in fasting insulin levels and insulin pulse amplitude months after the procedure (Gadir et al., 1990). Ovarian surgery did not alter the level of fasting glucose (Tulandi et al., 2000; Wu et al., 2000, 2004; Saleh et al., 2001; Duleba et al., 2003; Malkawi et al., 2003; Api

et al., 2005; Malkawi and Qublan, 2005). Insulin and glucose response to OGTT were modestly but significantly decreased after ovarian surgery in hyperinsulinaemic PCOS women only (Saleh et al., 2001). Combining the results of the lean and obese PCOS patients, the average OGTT did not change (Tulandi et al., 2000; Duleba et al., 2003). The insulin sensitivity index worsened in one study after the ovarian surgery (Duleba et al., 2003) and insulin/glucose decreased in another (Wu et al., 2000). Two studies showed unaltered glucose/insulin ratios (Wu et al., 2004; Api et al., 2005). The euglycemic–hyperinsulinaemic clamp was performed in one study and showed no difference in eight patients before and after ovarian surgery (although this study did not define its PCOS population) (Lemieux et al., 1999). Baseline parameters of women who achieved pregnancy after the surgery showed significant lower insulin levels and higher insulin sensitivity indexes prior to surgery compared with women who did not get pregnant (Duleba et al., 2003; Dale et al., 2004; Api et al., 2005).

Overall, insulin sensitivity does not seem to change after ovarian surgery, although more research is needed for more clarity. Hyperinsulinaemic women may become less (but remain) insulin resistant after surgery. The limitation of some of these studies is the exclusion of women who became pregnant before endocrine follow up, potentially resulting in selection bias. These pregnant women may have had more favourable insulin changes. Analysing the data from the normoinsulinaemic, hyperinsulinaemic, lean or obese women separately may reveal different results.

Leptin

Leptin is secreted by adipose tissue, modulates energy balance and influences reproductive function (Lonnqvist et al., 1995; Broberger, 2005). Leptin serum levels correlate positively with body mass index (BMI) (Lonnqvist et al., 1995; Telli et al., 2002) and obesity is associated with a resistance to leptin (Chan and Mantzoros, 2005). Insulin has been shown to stimulate leptin production (Kolaczynski et al., 1996) and there is evidence that androgens suppress leptin production (Jockenhovel et al., 1997; Remsberg et al., 2002). Many studies measured leptin levels in PCOS compared to weight matched controls. Most of these studies showed comparable leptin levels between PCOS and normal ovulatory women (Telli et al., 2002; Remsberg et al., 2002; Carmina et al., 2005), while others found higher leptin levels in PCOS (El et al., 1999; Baranowska et al., 1999). A relative leptin deficiency in overweight PCOS women is speculated, given the (visceral) fat mass and hyperinsulinaemia in these women (Remsberg et al., 2002). This relative leptin deficiency might (partly) be due to insulin resistance limiting insulin stimulated leptin secretion (Jacobs and Conway, 1999).

So far, the effect of surgery on leptin has been evaluated in one study, showing mean leptin levels comparable with pretreatment values 3 months after ovarian surgery. In obese PCOS

patients, leptin significantly decreased contrary to stable levels in lean PCOS women after ovarian surgery (Wu et al., 2004).

Renin

The renin-angiotensin system is classically known for its effects on blood pressure. Besides this effect on the circulation, it may also have an important role in reproduction (Vinson et al., 1997). In (normotensive) women with PCOS, elevated serum renin levels have been found compared with normal ovulatory women (Jaatinen et al., 1995; Hacihanefioglu et al., 2000).

Ovarian surgery did not influence renin levels significantly after the first menstrual cycle, measured in 11 PCOS patients (Anttila et al., 1998). It must be noted that total renin was measured. Changes in active renin concentrations could not be ruled out and local ovarian activity could have changed (Anttila et al., 1998).

Insulin-like growth factor and binding protein

Insulin-like growth factors (IGF) I and II have important roles in modulation of ovarian function (Fowler et al., 2000); IGF-I regulates a variety of processes in ovarian cells and stimulates androgen production (Carmina et al., 1995; Giudice, 1995). IGF binding globulins (IGFBP) influence the activity of IGFs in a cell- and tissue-specific manner (Beattie et al., 2006) and five of the six IGFBPs (IGFBP 1, 2, 3, 4 and 5) have been identified in the human ovary (Giudice et al., 1995). IGFBP-I alters serum IGF bioavailability and influences IGF-I action on the ovary (Fowler et al., 2000). Insulin is thought to act (partially) through ovarian IGF-I receptors, augmenting hyperandrogenism in PCOS (Gdansky et al., 1997). PCOS women have lower IGFBP-I concentrations compared with normal ovulatory women (Carmina et al., 1995).

IGF-I and IGFBP-I remained unchanged when measured 1–3 months after ovarian surgery in PCOS patients (Tiitinen et al., 1993; Amin et al., 2003; Wu et al., 2004). There are no publications on IGF-II and other IGFBP's levels before and after ovarian surgery in PCOS.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is secreted by the ovaries, has angiogenic properties and plays an important role in cyclic ovarian angiogenesis (Leung et al., 1989; Geva and Jaffe, 2000). VEGF levels are positively correlated with ovarian blood flow (Agrawal et al., 2002; bd El Aal et al., 2005). Elevated VEGF values have been found in women with PCO(S) (Agrawal et al., 1998, 2002; bd El Aal et al., 2005) and VEGF secretion is stimulated by LH, FSH and insulin in combination with hCG (Christenson and Stouffer, 1997; Agrawal et al., 2002).

Baseline VEGF levels were higher in PCOS women compared with normal ovulatory controls (Tulandi et al., 2000; Amin et al., 2003). Ovarian surgery lowered VEGF levels in combination with reduced ovarian stromal blood flow in one study of 25 PCOS patients (Amin et al., 2003). Another study showed no changes in VEGF concentrations after surgery in 27 PCOS patients (Tulandi et al., 2000). Results of the latter study may have been biased by the exclusion of six women who became pregnant before endocrine follow up.

Homocysteine

Homocysteine is a risk factor for atherosclerosis and has been found to be elevated in women with PCOS (Yarali et al., 2001; Loverro et al., 2002; Vrbikova et al., 2003), especially in insulin resistant individuals (Schachter et al., 2003; Wijeyaratne et al., 2004), although some studies have not found any difference (Sills et al., 2001; Morgante et al., 2002). It has been suggested that high homocysteine levels are linked to androgen levels (Vrbikova et al., 2003).

Homocysteine levels decreased 3 months after ovarian surgery, although this was measured in only one study of 22 PCOS patients (Kucuk and Kilic-Okman, 2005).

Lipid profile

Dyslipidaemia is common in patients with PCOS (Talbott et al., 1995; Orio, Jr. et al., 2004). PCOS women have higher total cholesterol, triglycerides and very low density lipoprotein and lower high-density lipoprotein (HDL) levels compared with ovulatory controls (Wild et al., 1985; Wild, 2002; Orio, Jr. et al., 2004; Vural et al., 2005).

Lipid levels did not seem affected by ovarian surgery. Ovarian surgery did not change total cholesterol, HDL and LDL concentrations in two studies (Duleba et al., 2003; Kucuk and Kilic-Okman, 2005).

DISCUSSION

When ovarian surgery causes damage to the PCOS ovaries, independent of the type of the procedure, the ovarian–pituitary-axis regulation changes. For optimal identification of essential endocrine changes after ovarian surgery, the endocrine events will be discussed in chronological order.

The day after surgery in PCOS patients, serum levels of ovarian produced steroids, and non-steroidal substances declined in combination with increased serum levels of pituitary hormones and increased pituitary sensitivity (Figure 8). Invariably lower serum levels of the ovarian hormones (testosterone, androstenedione, estradiol, inhibin) may (partially) be a direct effect

of the ovarian surgery. Apparently, granulosa and theca cell damage caused by the surgical procedure is responsible, possibly in combination with a temporary disruption of ovarian function. A consequence is altered ovarian feedback to the hypothalamus and pituitary, subsequently causing changes in pituitary sensitivity and secretion. This results in an increase of serum levels of pituitary hormones (LH, FSH, prolactin) shortly after the surgery. Both LH and FSH are normally suppressed by estrogens (Messinis, 2006), and the lower estrogen concentrations after ovarian surgery could augment the FSH and LH increase. In addition, FSH secretion is likely to be stimulated due to the fall of inhibin which normally restrains GnRH independent pituitary FSH secretion (Lambalk et al., 1998). However, a temporal change in secretion and sensitivity of the hypothalamus and pituitary induced by the anaesthesia or operation itself cannot be excluded. Temporally increased pituitary secretion has been found after surgery in regularly ovulating women (Messinis et al., 1999), although most studies found stable or even decreased pituitary hormone secretion after surgery in controls and PCOS patients (Adashi et al., 1980; Hagen et al., 1980).

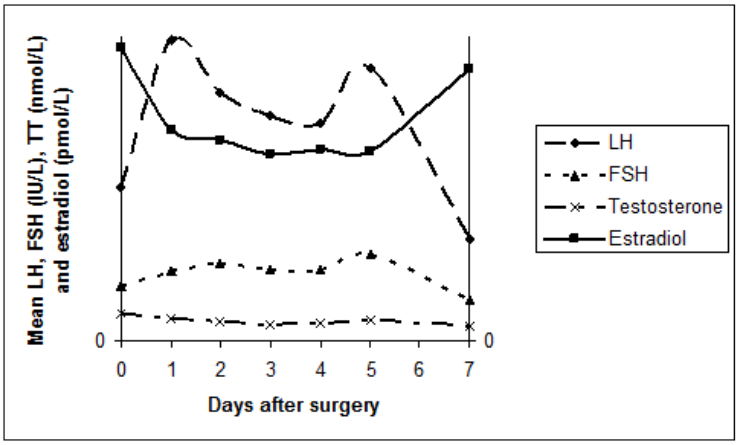

Figure 8. Mean levels of LH, FSH, testosterone (TT) and estradiol prior to ovarian surgery (days=0) and the first days following surgery in PCOS women. The figure is a compilation of Figures 1A, 3A, 5A and 6A.

A sufficient increase of FSH secretion can subsequently induce the growth of a follicle cohort, explaining the more distinct incline of FSH in responders compared with non-responders after surgery. Unfortunately, there are no studies reporting inhibin levels in the first hours after surgery, and therefore it is unclear if inhibin drops prior to the rise of FSH.

The LH levels that increase shortly after ovarian surgery are associated with increased pituitary sensitivity. The higher pituitary sensitivity occurs in combination with lower estrogen levels.

Estrogens normally exert a negative feedback on LH predominantly by blocking hypothalamic GnRH secretion, whereas pituitary sensitivity increases (Messinis, 2006). This more sensitive pituitary however does not secrete large amounts of LH because of the relative absence of endogenous GnRH. Lower estrogen levels after surgery are expected to diminish pituitary sensitivity, but possibly the remaining endogenous GnRH will temporarily provide enough substrate for increased LH production. It is also possible that sensitivity of the pituitary is increased by decreased secretion of GnSAF. GnSAF normally reduces pituitary sensitivity and suppresses LH secretion (Fowler et al., 2003). Ovarian cell damage by the surgery may cause a drop in the already-low GnSAF production immediately after the procedure, resulting in higher pituitary sensitivity thus explaining both the rise in LH levels and the increased pituitary response to GnRH. So far, GnSAF has not been purified, and although plausible, this GnSAF theory remains unproven.

With regard to prolactin, its elevation seen after surgery is probably related to stress of operation and/or anaesthetics, since elevation was seen in both PCOS patients and in regularly ovulatory controls, and a transitory prolactin elevation caused by surgical stress is a known phenomenon (Brandt et al., 1976; Adashi et al., 1980; Soules et al., 1980).

Besides changes in ovarian and pituitary hormone production, the adrenal production of DHEA(S) and 17-OH progesterone decreased in the first days after surgery. Because reduction of adrenal hormones is seen in PCOS women as well in regularly ovulating controls, a more general effect of surgery is suggested as a cause of this decrease.

Both PCOS patients and ovulatory controls show decreased DHT concentration the day after surgery. Lower circulating testosterone and androstenedione concentrations after ovarian surgery probably contribute to the lower DHT levels, as DHT is a peripheral product of these androgenic substrates.

Five days after the ovarian surgery, the ovarian production of estradiol and inhibin starts to rise after the initial reduction. These increments probably represent ovarian functional recovery and folliculogenenis. Synchronic with the estradiol elevation, FSH levels decrease (Figure 8). A plausible explanation for this suppression of FSH secretion are the higher estradiol and inhibin levels produced by growing follicles, a process similar to the normal ovulatory cycle (Jonard and Dewailly, 2004; Messinis, 2006). The elevated progesterone levels three weeks after ovarian surgery suggest that a proportion of the women were ovulating.

Reduced ovarian hormone production (testosterone, androstenedione, estradiol, inhibin) is seen in subsequent follicular phases after the ovarian surgery in PCOS. Previous studies have

shown that partial destruction of ovarian tissue due to the ovarian surgery results in a decreased ovarian reserve (Kandil and Selim, 2005). A decreased amount of ovarian tissue could result in less endocrine capacity and cause the reduction in ovarian hormone production.

Lower androgen levels after ovarian surgery are a known phenomenon. Destruction of androgen producing tissue in combination with lower LH levels after ovarian surgery is probably the main cause for this reduction. Besides lower androgen levels, SHBG increases modestly, possibly due to higher estradiol levels in ovulatory cycles (Eden et al., 1989). Increased SHBG levels result in lower levels of biologically active (free) androgens after surgery. Intra-ovarian hyperandrogenism is seen as the main culprit for follicle excess and arrest (Jonard and Dewailly, 2004), and lower androgen levels after ovarian surgery may reduce the follicle excess and facilitate appropriate folliculogenesis.

Lower ovarian production of inhibin B after ovarian surgery could be a reflection of the decreased ovarian reserve after the treatment, since inhibin B levels are a marker of follicular reserve (Tinkanen et al., 2001). So far, only limited data on inhibin are available.

Altered ovarian feedback through the reduced ovarian hormone production could be the cause of the restoration of pituitary function over time. Serum LH levels diminish, as its pulse amplitude decreases, in combination with a stable frequency. Weeks after the ovarian surgery, the pituitary sensitivity decreases, expressed by lower pituitary LH response to GnRH. Theoretically, restoration of GnSAF production by healthy growing follicles after surgery (Balen and Jacobs, 1994) in combination with decreased estradiol levels in the early follicular phases could result in diminished pituitary priming, consequently explaining the lower LH response to GnRH and the lower amplitude of pituitary LH secretion. Increased GnSAF production by growing follicles could also elucidate the lower LH levels found in responders compared with non-responders. Non-responders show no (adequate) follicle growth, resulting in less GnSAF production and higher LH levels.

Some time after surgery FSH levels become comparable to baseline values, in spite of lower inhibin B levels in the early follicular phase. Remarkably, such FSH levels were not able to initiate follicular growth before treatment, but after surgery these FSH levels are sufficient for folliculogenesis. This strongly suggests an increased effect of FSH after surgery. A more favourable endocrine environment may increase the ovarian sensitivity to FSH and in combination with an intercycle FSH rise, this may cause follicle growth to be induced. The endocrine environment may also be altered by changes in ovarian AMH tone. AMH levels are higher in PCOS compared with regularly ovulating women (Cook et al., 2002; Pigny et al., 2006) and reduction of the follicle excess and reserve after surgery could hypothetically reduce ovarian AMH production, resulting

in less AMH inhibition of FSH action. Ovarian sensitivity could therefore be increased by lower AMH production. FSH serum levels after surgery would become locally more effective, resulting in reversion of the follicular arrest.

The influence of ovarian surgery on adrenal hormones seems limited, as could be expected. Weeks to months after surgery cortisol, 17-OH progesterone levels and ACTH tests are comparable to pretreatment results and DHEA(S) is comparable or only slightly reduced. Resumption of ovulation after ovarian surgery seems independent of adrenal functional changes.

After the initial reduction, DHT levels return to pre-operative values or remain slightly lower. High peripheral conversion of testosterone, androstenedione and DHEA due to increased 5-alpha-reductase activity in PCOS could provide substantial DHT production in spite of reduced androgens. DHT normalization does not seem compulsory for induction of ovulation.

Insulin sensitivity does not seem to change after ovarian surgery, although hyperinsulinaemic women showed modest improvement. Assuming that an intrinsic defect in insulin action, the insulin androgenic pathway and *b*-cell dysfunction in PCOS are major contributors to insulin resistance (Dunaif et al., 1989; Ehrmann et al., 1995; Dunaif, 1997; Corbould et al., 2005), surgery is not expected to influence the hyperinsulinaemia and insulin resistance. Earlier studies showed that suppression of hyperandrogenism did not result in significant changes in insulin levels in hyperinsulinaemic, obese or lean PCOS women (Dunaif et al., 1990; Diamanti-Kandarakis et al., 1995) or lead to only modest improvements (Elkind-Hirsch et al., 1993; Moghetti et al., 1996). Reduction of androgen producing ovarian tissue and lower LH levels after surgery are apparently sufficient for reducing androgen levels, in spite of continuous stimulation of androgen production by insulin. However, a distinction has to be made between lean and obese PCOS patients: obese PCOS patients will have hyperinsulinaemia as a principal driver of ovarian hyperandrogenism and would probably benefit more from insulin lowering therapy, whereas lean PCOS patients would benefit from the lower LH levels found after ovarian surgery. Nevertheless, resolving the follicular arrest can occur without concomitant changes of the insulin metabolism.

Leptin, VEGF and homocysteine levels seem to decrease after ovarian surgery in PCOS, as reported by a few studies. Leptin decreased in obese subjects in spite of constant insulin levels, stable BMI and lower androgen levels. It is unknown how leptin secretion is attenuated in these obese PCOS women after the surgery. Lower VEGF levels may have been caused by lower LH concentrations, resulting in less VEGF stimulatory effects, in combination with a reduction of ovarian VEGF production due to decreased ovarian reserve after surgery (Kandil and Selim, 2005). Homocysteine levels decrease after ovarian surgery. The cause of this improvement

is unclear. It may be due to lower androgen levels, which are suggested to be linked with homocysteine levels (Vrbikova et al., 2003).

It has been suggested that IGF-I plays a role in the re-initiation of folliculogenesis (Balen and Jacobs, 1994). Local injury of the ovary could be followed by a cascade of inflammatory factors, among IGF-I (Balen and Jacobs, 1994), and IGF-I in turn would increase FSH action (Adashi et al., 1988) and follicular development could ensue. Looking at this hypothesis with the selected studies in mind, the studies measuring IGF-I or IGF-I BP concentrations after ovarian surgery all reported no changes (Tiitinen et al., 1993; Amin et al., 2003; Wu et al., 2004), but the IGF-I was measured month(s) after surgery. Assuming that the cascade of inflammatory factors will be diminished by that time, the results of the studies neither support nor reject this hypothesis. Furthermore, only IGF-II is expressed in the human ovary and it seems to play a more important role than IGF-I in normal follicular development (Giudice et al., 1995). Furthermore at this point in time, there is no convincing evidence that IGF system abnormalities have a central place in the follicular arrest in PCOS patients (Jonard and Dewailly, 2004).

The general limitation of using serum values remains the absence of information about the local ovarian changes, autocrine and interfollicular influences.

Conclusion

Endocrine changes after ovarian surgery for ovulation induction in PCOS seem to be governed by the ovaries. The rapid changes occurring after surgery strongly argue for inappropriate gonadotropin secretion secondary to inadequate ovarian feedback.

Reduction of all ovarian produced hormones immediately after surgery restores feedback to the hypothalamus and pituitary resulting in increased pituitary sensitivity and temporarily higher LH and particularly FSH levels. Initiation of folliculogenesis is induced by the increased FSH levels, in combination with a reduction of the follicle excess and reduced (intra-ovarian) androgenlevels.

In addition, upon ovarian surgery the endocrine environment changes over time. After the initial reduction, ovarian production of estradiol and inhibin increases, proving folliculogenesis. Subsequently through ovarian feedback, the sensitivity of the pituitary decreases and reduced FSH and LH levels are found. In addition, increased GnSAF production by growing follicles could explain the reduced pituitary sensitivity to GnRH, the lower LH levels and could antagonize the stimulatory effects of estradiol on GnRH-induced LH secretion (Fowler et al., 2003).

Continuous follicle growth in subsequent cycles after ovarian surgery occurs in a more favourable internal environment with less (free) androgens, lower LH levels, reduced follicle excess and

possibly lower local AMH production. This leads to a prolonged altered endocrine situation that seems to concord with increased ovarian sensitivity to FSH, since FSH levels comparable to pretreatment levels become adequate for inducing folliculogenesis after surgery.

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